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Commentary

Prophylactic Use of Chloroquine May Impair Innate Immune System Response against SARS-Cov-2

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In the last twenty years, betacoronaviruses have caused three global health-threatening diseases, including Severe Acute Respiratory Syndrome (SARS) in 2002, Middle-East Respiratory Syndrome (MERS) in 2012 and recently, a novel coronavirus-induced pneumonia, which was named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) in February, 2020. A serious outcome of COVID-19 in some patients is Acute Respiratory Distress Syndrome (ARDS) that may be fatal.[1,2] Given the severity of COVID-19, a desperate global research effort is underway to identify effective antiviral therapies.

Chloroquine, that was discovered in 1934, and its derivative hydroxychloroquine, are attracting considerable attention as potential therapies for COVID-19. They are in widespread clinical use as generic medications for the treatment and prevention of malaria, as well as for auto-immune diseases such as rheumatoid arthritis and systemic lupus erythematosus.[3] In recent months, they have become popular as potential therapies for COVID-19. Their use is based on in vitro data showing that they exert a broad-spectrum antiviral activity against a wide range of viruses, including coronavirus.[4] Despite the lack of robust clinical evidence of antiviral efficacy, they are widely advocated for the treatment of COVID-19, as well as in prophylactic regimens in healthy individuals to prevent coronavirus transmission.[5,6] As will be discussed in this commentary, their safety and effectiveness may be compromised by their interference with the body's normal salutary immune response.

The innate immune system is an intrinsic defense mechanism against invading pathogens and acts as the first line of defense to prevent viral invasion and subsequent replication. It is equipped with receptors, commonly termed pattern recognition receptors (PRRs) that are capable of recognizing microbial pathogens due to the presence of pathogen-associated molecular patterns (PAMPs). PAMPs include various microbial molecules such as viral nucleic acid and viral envelop proteins. One of the largest and best-studied families of PRRs in detecting PAMPs of viruses and other pathogens are Toll-like Receptors (TLRs).[7-9] To date, 13 murine and 10 human subtypes of TLRs have been identified.[10] TLRs can be divided into two main groups: 1) plasma membrane TLRs (TLR1, 2, 5, 6 and 10-11) which are expressed on the extracellular surface of cells and recognize PAMPs on the surface of invading microbes, and 2) intracellular TLRs, often termed nucleic acid sensors (TLR3, 7, 8 and 9), that are expressed on the membrane of intracellular vesicles. TLR4 can be expressed on both cellular and endosomal membranes.[11]

Endosomal TLRs (TLR3, 7, 8 and 9) identify viral nucleic acids and, along with TLR4, are critical in the recognition of viral genetic materials and for the initiation of antiviral responses.[9] Of these, TLR3 binds to viral double-stranded RNA (dsRNA) whereas TLR7 and 8 bind to viral single-stranded RNA (ssRNA).[8] The spike (s) protein and single-strand RNA (ssRNA) have been proposed as key PAMPs in SARS-CoV. It's important to note that coronaviruses are enveloped viruses that contain a positive-sense single-stranded RNA genome1 and their recognition in the endosome by endosomal TLRs is dependent on acidification of the endosomal vesicles.[8,12] When a TLR recognizes a PAMP, the host rapidly activates an innate immune response which triggers the release of interferons (IFNs) and inflammatory cytokines and chemokines in order to inhibit virus replication and eliminate the invading pathogen.[8] While the proper functioning of the immune system protects the body from pathogens, overexpression and exhaustion of the adaptive immune system, rather than the innate immune response, is mainly responsible for the cytokine storm associated with the severe manifestations of COVID-19. When the body is exposed to the virus, the innate immune system limits viral spread within the host and therefore plays a protective role during the initiation of the infection or in mild COVID-19 disease, although, under conditions of high viral load, the innate immune response can also provoke immune-related pathology resulting in severe pneumonia.

Several studies have reported protective and therapeutic effects of activators of TLRs in viral diseases. TLR3 agonists exert protective effects against several viruses.[9] The TLR7 agonist, imiquimod, is approved for the treatment of genital warts caused by human papillomavirus infection. In addition, ANA-773, a prodrug of isatoribine and a TLR7 agonist, has been developed for the treatment of HCV-infected patients and its efficacy is demonstrable in

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hepatitis C patients.[8,13]

An important requirement for the antiviral effectiveness of TLR activation is the acidic environment of endosomes. However, both chloroquine and hydroxychloroquine are weak bases and one of their antiviral mechanisms is attributed to an elevation of pH of acidic intracellular organelles, such as endosomes and lysosomes.[3] Thus, it is possible that the alkalization of these compartments by chloroquine or hydroxychloroquine may limit TLR signaling, thereby impairing the effectiveness of the body's natural defense mechanisms. Indeed, in agreement with this hypothesis, the prophylactic use of chloroquine exacerbates acute Chikungunya virus infection in a non-human primate model.[14]

In summary, TLRs function as key components of the innate immune system require the acidic environment of endosomes to produce their antiviral effects. In contrast, the antiviral actions of chloroquine are partially attributed to an increment in pH of endosomes that may limit the beneficial actions of TLR activation. Therefore, we propose that the use of chloroquine as a prophylaxis approach to reduce COVID-19 transmission, particularly in immunosuppressed individuals, may actually be detrimental and facilitate the initiation and development of COVID-19. Clinical studies will be required to clarify this important issue.

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Conflict of Interest

The authors declare they have no conflict of interest.

References

1. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020;10(2):102-8. doi:10.1016/j.jpha.2020.03.001
2. Liu C, Zhou Q, Li Y, Garner LV, Watkins SP, Carter LJ et al. Research and development on therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases. ACS Central Science. 2020;6:315-31. doi:10.1021/acscentsci.0c00272
3. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020; 6:16. doi:10.1038/s41421-020-0156-0
4. Guo D. Old weapon for new enemy: drug repurposing for treatment of newly emerging viral diseases. Virol Sin. 2020;35(3):253-5. doi:10.1007/s12250-020-00204-7
5. Pagliano P, Piazza O, De Caro F, Ascione T, Filippelli A. Is Hydroxychloroquine a possible post-exposure prophylaxis drug to limit the transmission to health care workers exposed to COVID19? Clin Infect Dis. 2020; 71(15):887-8. doi:10.1093/cid/ciaa320
6. Mitja O, Clotet B. Use of antiviral drugs to reduce COVID-19 transmission. Lancet Global Health. 2020; 8(5):e639-40. doi:10.1016/S2214-109X(20)30114-5
7. Abdul-Cader MS, Amarasinghe A, Abdul-Careem MF. Activation of toll-like receptor signaling pathways leading to nitric oxide-mediated antiviral responses. Arch Virol. 2016;161(8):2075–86. doi:10.1007/s00705-016-2904-x
8. Lester SN, Li K. Toll-Like Receptors in antiviral innate immunity. J Mol Biol. 2014;426(6):1246-64. doi:10.1016/j.jmb.2013.11.024
9. Patel MC, Shirey KA, Pletneva LM, Boukhvalova MS, Garzino-Demo A, Vogel SN, et al. Novel drugs targeting Toll-like receptors for antiviral therapy. Future Virol. 2014; 9(9):811-29. doi:10.2217/fvl.14.70
10. Soraya H, Clanachan AS, Rameshrad M, Maleki-Dizaji N, Ghazi-Khansari M, Garjani A. Chronic treatment with metformin suppresses toll-like receptor 4 signaling and attenuates left ventricular dysfunction following myocardial infarction. European Journal of Pharmacology. 2014; 737:77-84. doi:10.1016/j.ejphar.2014.05.003
11. El-Zayat SR, Sibaii H, Mannaa FA. Toll-like receptors activation, signaling, and targeting: an overview. Bull Natl Res Cent. 2019;43:187. doi:10.1186/s42269-019-0227-2
12. Lund JM, Alexopoulou L, Sato A, Karow M, Adams NC, Gale NW, et al. Recognition of single-stranded RNA viruses by Toll-like receptor 7. Proc Natl Acad Sci U S A. 2004;101(15):5598-603. doi:10.1073/pnas.0400937101
13. Es-Saad S, Tremblay N, Baril M, Lamarre D. Regulators of innate immunity as novel targets for panviral therapeutics. Curr Opin Virol. 2012;2(5):622-8. doi:10.1016/j.coviro.2012.08.009
14. Roques P, Thiberville SD, Dupuis-Maguiraga L, Lum FM, Labadie K, Martinon F, et al. Paradoxical effect of chloroquine treatment in enhancing chikungunya virus infection. Viruses. 2018;10(5):268 doi:10.3390/v10050268